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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
Before the Board of Patent Appeals and Interferences

In re PATENT APPLICATION OF

FERGUSON Atty. Ref.: 39-196

Serial No.: 09/459,979 Group Art Unit: 1646

Filed: December 14, 1999 Examiner: Jiang, D.

For: PHARMACEUTICAL COMPOSITION CONTAINING INHIBITORS OF INTERFERON-GAMMA

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November 12, 2002

APPEAL BRIEF

Hon. Commissioner of Patents
and Trademarks
Washington, DC 20231

Sir:

This is an appeal from the final rejection of claims 39-43. No claim stands allowed.

REAL PARTY IN INTEREST

The real party in interest in this application is Renovo Limited, Manchester, United Kingdom.

RELATED APPEALS AND INTERFERENCES

No other appeals or interferences are known to Appellant, Appellant's legal representative, or assignee that will directly affect or be directly affected by or

have a bearing on the Board's decision in the pending appeal.

STATUS OF THE CLAIMS

Claims 39-43 are pending in this application and have been finally rejected. Claims 1-24 were cancelled and claims 25-32 were added in the Preliminary Amendment filed December 14, 1999. Claims 25-32 were cancelled and claims 33-38 were added in the Amendment filed May 17, 2001. Claims 33-38 were cancelled and claims 39-45 were added in the Amendment filed January 31, 2002. Claims 44 and 45 were cancelled in the Amendment Under Rule 116 filed September 10, 2002. The claims on appeal are set forth in the attached Appendix.

STATUS OF THE AMENDMENTS

An Amendment Under Rule 116 was filed on September 10, 2002, in response to the final rejection of April 10, 2002. The claim cancellations set forth in that Amendment have been entered.

SUMMARY OF THE INVENTION

The present invention (as claimed in claim 39 and claims depending therefrom) relates to a method for promoting the healing of a chronic wound in a patient. The

method comprises administering to the patient an amount of a stimulator of IFN-γ sufficient to effect the promotion of healing of the chronic wound.

Support for the invention is found throughout the application including, for example, at page 4, line 20, to page 5, line 16, and at page 6, lines 3-6.

The foregoing represents a concise summary of the invention.

THE ISSUES

Claims 39-43 stand rejected under 35 USC 103 over Mustoe et al (J. Clin. Invest. 87(2):694-703 (1991)) and Badgett et al (J. Lipid Mediators Cell Signaling, 13(1):89-97 (1996)).

Accordingly, the sole issue present for review is whether claims 39-43 would have been obvious over Mustoe et al in combination with Badgett et al.

GROUPING OF THE CLAIMS

The claims stand or fall together.

ARGUMENTS

Reversal of the rejection of the claims as obvious is requested for the reasons that follow.

The Examiner contends that Badgett et al teaches that PDGF is a potent mediator of fibroblast proliferation and chemotaxis. The Examiner further contends that it is known that IFN-γ primes macrophages to increase PDGF production. The Examiner summarizes the teachings of Badgett et al as showing that there is a clear concentration-dependent priming effect of IFN-γ on the secretion of macrophage derived PDGF, and that treatment of macrophages with 10,000U/ml IFN-γ results in a five-fold increase in PDGF release, while lower concentrations of IFN-γ (under 1000 IU) block PDGF-induced fibroblast proliferation.

Appellant submits that the Examiner's interpretation of the teachings of Badgett et al, and, in particular, of the effects of IFN-γ on fibroblast proliferation reported therein, is incorrect. In fact, Appellant submits that Badgett et al actually teaches away from the instant invention for the following reasons:

1. Badgett et al provides that IFN-γ inhibits fibroblast proliferation in a dose-dependent fashion, even in the presence of PDGF.

2. The teachings of Badgett et al regarding the ability of IFN-γ to prime increased PDGF release in the

presence of iron particles are not applicable to the biology of chronic wound healing.

3. Badgett et al clearly shows that in the absence of iron priming, treatment with IFN-γ does not cause a dose-dependent increase in PDGF release.

The foregoing points are considered in greater detail below.

Interferon-γ treatment inhibits fibroblast proliferation

Based on the Examiner's interpretation of the teachings of Badgett et al, he/she contends that it would have been obvious to a person skilled in the art to treat chronic wounds with "higher" doses of IFN-γ (as recited in claim 41) on the basis that "IFN-γ stimulates PDGF production in a dose dependent fashion, and the lower dose would block PDGF-induced fibroblast proliferation".

Appellant respectfully submits that the Examiner's contention overlooks Badgett et al's findings on the effect of IFN-γ on fibroblast growth. The teaching of Badgett et al is that all doses of IFN-γ inhibit fibroblast proliferation, and higher doses of IFN-γ cause significantly greater inhibition. Given that chronic wound healing requires fibroblast proliferation, Badgett et al would not have been considered suggestive of the subject invention.

The results of Badgett et al clearly illustrate the dose-dependent anti-proliferative effects of IFN-γ. This finding is of such significance that it is reported in lines 10 and 11 of the abstract, which state that "when IFN-γ was added to quiescent rat lung fibroblasts (RLFs) in the presence of PDGF-BB, the cytokine induced a concentration-dependent decrease in cell growth".

Badgett et al further notes "our data indicate that the early passage lung fibroblasts which normally respond vigorously to PDGF were inhibited from dividing by the IFN-γ treatment" (page 96, lines 2 and 3). Badgett et al suggests that this anti-proliferative effect may result from the fact that, as shown in previous studies, "IFN-γ [inhibits] the expression of PDGF-induced *c-myc* and *c-fos* (Einat et al, 1985) two genes believed to play a central role in the mechanism controlling PDGF-mediated cell division" (page 95, lines 19-21).

Significantly, the results of Badgett et al show that high doses of IFN-γ are anti-proliferative for fibroblasts, even in the presence of PDGF. For example, Figure 3 of the citation shows the results of treatment of rat lung fibroblasts, cultured in the presence of 15ng/ml PDGF, with increasing concentrations of IFN-γ. These results clearly

show that treatment with 10, 50 and 100U/ml IFN-γ significantly decreases fibroblast replication compared to controls ($P<0.05$), and that treatment with 1000U/ml IFN-γ had an even more pronounced anti-mitotic effect ($P<0.01$).

The doses of IFN-γ used in Badgett et al have a significant anti-proliferative effect, and these doses are markedly lower than those considered in the instant application (doses in the range of 7,500 to 15,000 IU). The skilled person, on reading Badgett et al, would thus have been led to conclude that treatment with dosages of IFN-γ referenced in the instant application would have significantly decreased fibroblast proliferation and so would have been detrimental to the healing of a chronic wound. This is the opposite of what Appellant observed - Appellant found that application of IFN-γ promoted wound healing.

Therefore, rather than having rendered the instant claims obvious (as the Examiner contends), Badgett et al would, in fact, would have taught away from present invention.

The in vitro model of lung disease is not applicable to chronic wound healing

The Examiner states that "there is a clear concentration-dependent priming effect of IFN-γ on the secretion of macrophage-derived PDGF, and at 10000U/ml, IFN-γ causes a more than 5-fold increase in PDGF release". However, the skilled person would have appreciated that there are many differences between wound healing, such as chronic wound healing, and the *in vitro* model of lung disease employed by Badgett et al. Appellant respectfully submits that these differences are such that a skilled person could not have expected the five-fold increase in release referred to by the Examiner to occur during chronic wound healing.

The five-fold increase in PDGF release by cultured macrophages (shown in Figure 2 of Badgett et al) is only exhibited by macrophages that have undergone pre-treatment with IFN-γ prior to stimulation by iron particles. This stimulation with iron particles is specific to the model of lung disease used by Badgett et al. In this model, the iron particles replicate macrophages' uptake of particles in conditions such as asbestosis and silicosis. The skilled person would have immediately appreciated that such

iron stimulation does not occur during the healing of chronic wounds, and would thus have expected that the priming effect (and associated increase in PDGF release) would not have occurred in a wound healing context.

In the absence of iron priming IFN-γ treatment does not cause a dose-dependent increase in PDGF release

The Examiner's contention that Badgett et al teaches "that IFN-γ stimulates PDGF production in a dose dependent fashion" is not supported by the disclosure of the citation. In fact, Badgett et al show that (in the absence of iron priming, which is not applicable to chronic wound healing for the reasons set out above) IFN-γ treatment does not cause a dose-dependent increase in PDGF release.

Figure 1 of Badgett et al illustrates that the production of PDGF in response to IFN-γ treatment without iron priming is not dose dependent. The maximal level of PDGF produced in the absence of iron priming, around 4ng/ml as illustrated in Figure 1, is elicited by treatment with either 100U or 1000U IFN-γ. This suggests that PDGF production in response to IFN-γ treatment reaches a plateau at IFN-γ dosages of around 100U or less. Thus the skilled person would not have had any expectation that higher doses of IFN-γ, as contemplated in the instant specification,

would have had any greater utility in eliciting PDGF release than lower doses.

The maximal concentration of PDGF released by un-primed macrophages in response to IFN-γ treatment (about 4ng/ml PDGF) is considerably lower than the 15ng/ml PDGF used in the *in vitro* study of fibroblast proliferation. Since the anti-proliferative effects of IFN-γ are sufficient to overcome the mitogenic activity of the higher concentration of PDGF (15ng/ml), a skilled person would have had absolutely no reason to expect that the smaller quantities of PDGF released by macrophages treated with IFN-γ would have been sufficient to stimulate fibroblast proliferation and wound healing.

Summarizing the foregoing:

1. The skilled person, on reading Badgett et al, would had recognized that IFN-γ inhibits fibroblast proliferation in a concentration dependent manner. An artisan would therefore have expected that administration of IFN-γ to a chronic wound would have inhibited fibroblast proliferation, thereby inhibiting wound healing. Accordingly, the present invention would have been surprising in light of Badgett et al, since chronic wound

healing requires the stimulation of fibroblast proliferation.

2. The skilled person would have appreciated that the model used by Badgett et al is specific to lung disease and produces effects that are not seen during the healing of chronic wounds (i.e., iron priming and the subsequent increase in release of PDGF). Accordingly an artisan would not have expected the teachings of Badgett et al to be applicable to chronic wound healing.

3. IFN-γ does not have a dose-dependent effect on PDGF release. The skilled person would thus have realized that the amount of PDGF likely to be released by macrophages in response to IFN-γ treatment would not have been sufficient to counteract the anti-proliferative effects of the IFN-γ itself.

As indicted above, the teachings of Badgett et al are not relevant to, nor would they have been suggestive of, the instant invention. Thus, it is submitted that one skilled in the art would not have been motivated to combine Badgett et al with Mustoe.

Mustoe et al's teaching that PDGF is a growth factor that has significant activity in the tissue repair process would not have cured the above-described fundamental

failings of Badgett et al. Nothing is found in Mustoe et al relating to IFN-γ, much less anything suggestive of the ability of IFN-γ to promote the healing of a chronic would.

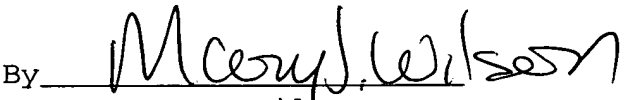
Given the above-referenced teachings of Badgett et al that would have resulted in an artisan expecting administration of IFN-γ to inhibit fibroblast proliferation (thereby inhibiting wound healing), no basis is seen for the Examiner's assertion that the present invention would have been obvious over a combination of Mustoe et al, which says nothing of IFN-γ, and Badgett et al.

* * *

In view of the above, reversal of the rejection is clearly in order and same is requested.

Respectfully submitted,

NIXON & VANDERHYE, P.C.

By 
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APPENDIX

39. A method for promoting the healing of a chronic wound in a patient comprising administering to said patient an amount of a stimulator of IFN-γ sufficient to effect the promotion of healing of said chronic wound.

40. The method according to claim 39, wherein said stimulator of IFN-γ is administered to a site of wounding.

41. The method according to claim 39, wherein between 7,500 and 15,000 IU IFN-γ is administered.

42. The method according to claim 39 wherein said stimulator of IFN-γ is selected from the group consisting of IFN-γ and a partially modified form of IFN-γ.

43. The method according to claim 39 wherein the stimulator of IFN-γ is administered in combination with a pharmaceutically acceptable carrier, diluent or excipient.